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Urate, Blood Pressure, and Cardiovascular Disease

Evidence From Mendelian Randomization and Meta-Analysis of Clinical Trials

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ABSTRACT: Serum urate has been implicated in hypertension and cardiovascular disease, but it is not known whether it is exerting a causal effect. To investigate this, we performed Mendelian randomization analysis using data from UK Biobank, Million Veterans Program and genome-wide association study consortia, and meta-analysis of randomized controlled trials. The main Mendelian randomization analyses showed that every 1-SD increase in genetically predicted serum urate was associated with an increased risk of coronary heart disease (odds ratio, 1.19 [95% CI, 1.10–1.30]; $P=4\times 10^{-6}$), peripheral artery disease (1.12 [95% CI, 1.03–1.21]; $P=9\times 10^{-3}$), and stroke (1.11 [95% CI, 1.05–1.18]; $P=2\times 10^{-4}$). In Mendelian randomization mediation analyses, elevated blood pressure was estimated to mediate approximately one-third of the effect of urate on cardiovascular disease risk. Systematic review and meta-analysis of randomized controlled trials showed a favorable effect of urate-lowering treatment on systolic blood pressure (mean difference, -2.55 mmHg [95% CI, -4.06 to -1.05]; $P=1\times 10^{-3}$) and major adverse cardiovascular events in those with previous cardiovascular disease (odds ratio, 0.40 [95% CI, 0.22–0.73]; $P=3\times 10^{-3}$) but no significant effect on major adverse cardiovascular events in all individuals (odds ratio, 0.67 [95% CI, 0.44–1.03]; $P=0.07$). In summary, these Mendelian randomization and clinical trial data support an effect of higher serum urate on increasing blood pressure, which may mediate a consequent effect on cardiovascular disease risk. High-quality trials are necessary to provide definitive evidence on the specific clinical contexts where urate lowering may be of cardiovascular benefit. (*Hypertension*. 2020;77:00-00. DOI: 10.1161/HYPERTENSIONAHA.120.16547.)

• Data Supplement

Key Words: blood pressure ■ cardiovascular diseases ■ odds ratio ■ systematic review ■ uric acid

Urate is a breakdown product of purine metabolism. Its raised levels have been associated with a number of adverse health outcomes including gout, hypertension, and cardiovascular disease (CVD).¹ However, it remains unclear whether these associations represent causal effects.^{2,3} The relationship between serum urate, obesity, diet, and other cardiovascular risk factors raises considerable potential for confounding and reverse causation.⁴

The genetic determinants of serum urate levels have been increasingly well-characterized.⁴ This has made it possible to identify better instruments for Mendelian randomization (MR) analyses investigating the effect of genetically predicted serum urate on cardiovascular outcomes than in previous efforts.^{3,5–7} The use of variants randomly allocated at conception to proxy the effect of modifying serum urate means that MR is less susceptible

Novelty and Significance

What Is New?

- This study found that higher genetically predicted serum urate was associated with an increased risk of cardiovascular disease, with elevated blood pressure mediating approximately one-third of this effect.
- Meta-analysis of randomized controlled trials showed a favorable effect of urate lowering on systolic blood pressure and cardiovascular events in those with previous cardiovascular disease but no significant effect on cardiovascular events in all individuals.

What Is Relevant?

- Lowering serum urate may represent a therapeutic target for reducing blood pressure and risk of cardiovascular disease.

Summary

Genetic analyses and clinical trial data support an effect of higher serum urate on increasing blood pressure, which may mediate a consequent effect on cardiovascular disease risk. High-quality trials are necessary to provide definitive evidence on the specific clinical contexts where urate lowering may be of cardiovascular benefit.

Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
FAST	Febuxostat and Allopurinol Streamlined Trial
GWAS	genome-wide association study
HEART	Allopurinol and Cardiovascular Outcomes in Patients With Ischaemic Heart Disease
IVW	inverse-variance weighted
MACE	major adverse cardiovascular event
MR	Mendelian randomization
OR	odds ratio
PAD	peripheral artery disease
RCT	randomized controlled trial
SBP	systolic blood pressure

to the environmental confounding, measurement error, and reverse causation bias that can limit causal inference in traditional epidemiological approaches.

Preclinical studies support a causal role for urate in hypertension.⁸ Randomized controlled trial (RCT) data have shown that both allopurinol and probenecid reduce systolic blood pressure (SBP) in hyperuricemic adolescents.^{1,9,10} Pooling of all available trial data can

updated systematic review and meta-analysis of urate-lowering RCTs.

METHODS

All data used in this work are either publicly accessible or available on request from their original studies, which obtained appropriate patient consent and ethical approval. The UK Biobank data were accessed through application 236. All results generated in this work are presented in either the article or its [Data Supplement](#).

Two-Sample MR

The MR analyses have been reported as per the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian randomization guidelines.¹²

Genetic Association Estimates

Genetic association estimates for serum urate in 2-sample MR were obtained by using the PLINK software to meta-analyze summary data from genome-wide association study (GWAS) analyses of 110347 European-ancestry individuals and 343836 White British UK Biobank participants, respectively.^{13–15} Urate estimates in MR analyses are provided per 1-SD increase, which corresponds to 80.3 $\mu\text{mol/L}$. For consideration of SBP (or diastolic blood pressure/pulse pressure) as a mediator in the 2-sample multivariable MR, genetic association estimates were obtained from a GWAS

outcome to avoid overlap with the UK Biobank participants used to obtain genetic association estimates for urate, as this can bias MR estimates.¹⁸ SBP estimates are provided per 1-SD increase, which corresponds to 18.6 mmHg. Genetic association estimates for CHD were obtained from the CARDIoGRAMplusC4D Consortium 1000G multiethnic GWAS (77% European ancestry) of 60 801 cases and 123 504 controls, with a broad and inclusive definition of CHD applied.¹⁹ Genetic association estimates for peripheral artery disease (PAD) were obtained from the Million Veterans Program multiethnic (72% European ancestry) GWAS of 31 307 cases and 211 753 controls, with case definitions made using hospital diagnosis and procedure codes.²⁰ Genetic association estimates for stroke were obtained from the MEGASTROKE multiethnic (86% European ancestry) GWAS of 67 162 cases and 454 450 controls,²¹ with the stroke definition including both ischemic and hemorrhagic etiologies. Genetic association estimates for ischemic stroke only (60 341 cases and 454 450 controls) were used in secondary analyses.²¹

Genetic Variants Used as Instruments

Genetic instruments for the 2-sample MR were identified as single-nucleotide polymorphisms that were associated with urate (or SBP, in mediation analyses) at genome-wide significance ($P < 5 \times 10^{-8}$) and were in pair-wise linkage disequilibrium with $r^2 < 0.001$. Clumping was performed using the TwoSampleMR package of R.²² For univariable MR, instrument strength was estimated using the F statistic, with variance in the exposure explained assessed using the R^2 value.²³

Statistical Analysis

In all analyses, single-nucleotide polymorphisms were aligned by their effect alleles, and no additional consideration was made for palindromic variants. Two-sample MR analyses were performed to investigate the effect of genetically predicted serum urate on CHD, PAD, stroke, and SBP, respectively. A Bonferroni threshold ($P < 0.01$) that corrected for multiple testing related to the 4 outcomes was used to ascertain statistical significance in the main analysis. Inverse-variance weighted (IVW) MR was used in the main analysis, with the simple median, contamination mixture method, Egger, pleiotropy residual sum and outlier,²⁴ and multivariable MR²⁵ (only for CVD outcomes) sensitivity analyses used to explore the robustness of the findings to potential pleiotropy of the genetic variants. Given the previously demonstrated overlap in the genetic determinants of urate with other metabolic traits,⁴ the multivariable MR sensitivity analysis adjusted for genetic associations of the instruments with body mass index, esti-

cardiovascular outcome that is mediated through SBP.²⁶ SEs were estimated using the propagation of error method.

To investigate potential effects of the cardiovascular traits on serum urate levels, we also performed IVW MR analyses considering genetically predicted CHD, PAD, stroke, and SBP as exposures and serum urate levels as the outcome. The approach taken was as described above, except that the considered exposure and outcome were switched.

Further details on the 2-sample MR analyses are provided in Methods in the [Data Supplement](#). Statistical analyses for the 1-sample MR are detailed in Methods in the [Data Supplement](#) and Table S1 in the [Data Supplement](#).

Systematic Review and Meta-Analysis of RCTs

The systematic review was conducted in accordance with the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.²⁷ The study protocol was registered and published in the International Prospective Register of Systematic Reviews (CRD42020164589).

Inclusion and Exclusion Criteria

RCTs of pharmacological urate-lowering versus placebo or no treatment of duration ≥ 28 days in patients ≥ 18 years of age were eligible. Studies with cointervention that was inconsistent between intervention and control groups or with mixed experimental groups were excluded.

Data Sources and Searches

We conducted a systematic search of multidisciplinary databases across 4 electronic platforms: Medline (Ovid), Embase (Ovid), Web of Science (Thomson Reuters), and Cochrane Library (Cochrane). Studies published from January 1, 2016, to September 30, 2019, were considered. The literature search terms matched those used in a previous systematic review (Methods in the [Data Supplement](#)).¹⁰ No language restrictions were applied. Reference lists of retrieved articles were reviewed to identify additional relevant articles. Data were included from studies in previous systematic reviews investigating the effects of urate-lowering therapy on SBP (searches until June 29, 2016)¹¹ and CVD (searches until December 30, 2016).⁷

Data Extraction

Study details and results were extracted using a predesigned template. In the case of crossover trials, only data from the first study period (before crossover) were used. Risk of bias was assessed in accordance with the Cochrane guidelines.²⁸

cardiovascular event (MACE; cardiovascular death, nonfatal myocardial infarction, unstable angina requiring urgent revascularization, or nonfatal stroke). In secondary analysis, we also considered MACE in patients with prior CVD, as this would likely represent a higher risk population, thus potentially offering greater statistical power.

Statistical Analysis

Analysis of extracted data was based on modified intention-to-treat (considering patients who received at least 1 dose of the allocated treatment) or intention-to-treat results. If not reported, the mean change in SBP pre- and post-treatment was calculated and the SD was imputed using the propagation of error method using a correlation coefficient that was derived from the largest study in the meta-analysis that reported SD for SBP values at baseline, at end of the study, and for the change in SBP.^{29,30} The measure of effect size was the difference in mean SBP, defined as the mean difference between patients treated with urate-lowering therapy versus control. A negative value of the difference in mean SBP indicates a greater reduction of SBP in the urate-lowering therapy group as compared with the control group. Overall CVD risk estimates are described in terms of odds ratio (OR).

Random-effects IVW meta-analysis was used to pool estimates from different studies, and study heterogeneity was assessed using the I² statistic. Cochran Q test was used to investigate heterogeneity between the meta-analysis estimates obtained for risk of MACE in all patients as compared with those with previous CVD. Sensitivity

analyses were conducted including only studies at low risk of bias. For the analysis considering SBP as an outcome, meta-regression was performed to assess the effect of baseline SBP on treatment response. Meta-regression analyses were also performed to assess the associations of baseline serum urate concentration, absolute change in serum urate concentration, and proportional change in serum urate concentration with treatment response for changes in SBP and risk of MACE in all patients. Analyses were conducted using the Comprehensive Meta-Analysis software, version 3 (Biostat).

RESULTS

Mendelian Randomization

The instruments for urate that were used in the 2-sample MR are presented in Table S2. The main IVW MR showed that higher genetically predicted serum urate levels were associated with an increased risk of CHD, with OR of 1.19 ([95% CI, 1.10–1.30] *P*=4×10^{−5}) per 1-SD increase in genetically predicted urate. Consistent results were obtained in all MR sensitivity analyses except MR-Egger, which had wide 95% CIs (Figure 1). Higher genetically predicted serum urate was also associated with increased risk of both PAD (OR, 1.12 [95% CI, 1.03–1.21]; *P*=9×10^{−3}) and stroke (OR, 1.11 [95% CI, 1.05–1.18]; *P*=2×10^{−4}) in the main IVW analysis, with similar results obtained in all MR sensitivity analyses

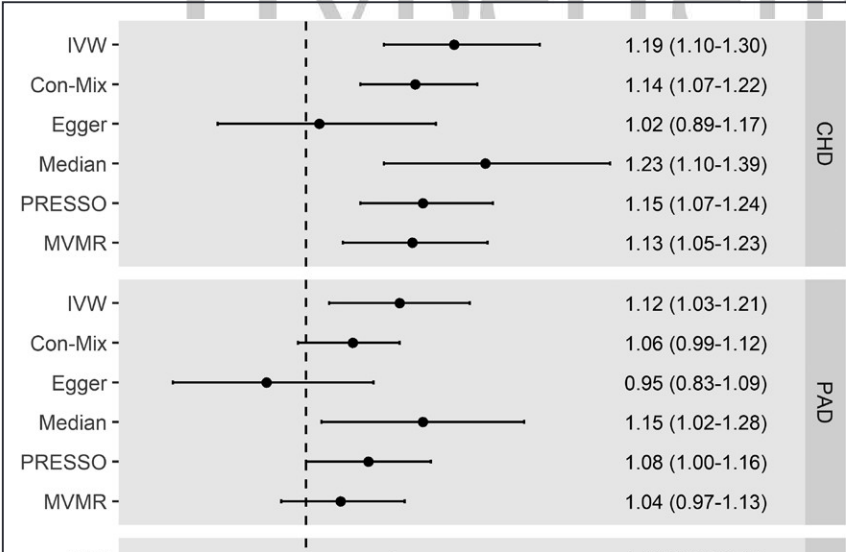


Figure 1. Mendelian randomization estimates for the effect of 1-SD increase in genetically predicted serum urate levels on risk of coronary heart disease (CHD), peripheral artery disease (PAD), and stroke. Multivariable Mendelian randomization (MVMR) adjusting for genetic associations of the instrument variants with body mass index, estimated glomerular filtration rate, type 2 diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. The outlier-corrected pleiotropy residual sum and outlier (PRESSO) results are presented (5 outlier variants were identified for CHD, 8 for PAD, and 1 for stroke). The Egger

except MR-Egger, which again had wide 95% CIs (Figure 1). For the multivariable MR adjusting for genetic confounding through body mass index, estimated glomerular filtration rate, type 2 diabetes, and lipid traits, direct effects of these exposures on risk of the respective CVD outcomes are presented in Table S3. Considering SBP, the main IVW and sensitivity MR analyses all provided supporting evidence of a causal effect of serum urate (IVW estimate in SD units per 1-SD increase in genetically predicted urate, 0.09 [95% CI, 0.05–0.12]; $P=6\times 10^{-7}$; Figure 2). Scatter plots depicting the association of the instrument variants with serum urate and the respective outcomes are presented in Figures S1 through S4.

Performing multivariable MR to adjust for genetically predicted SBP showed attenuation of the urate effect estimates for the CVD outcomes as compared with the main IVW univariable MR (Figure 3), supporting that part of the effect of urate on these outcomes is mediated through SBP. Similar results were obtained when considering diastolic or pulse pressure as mediators (Figure S5) or when considering only ischemic stroke rather than all stroke as an outcome (Figure S6). Network MR mediation analysis quantified this as 29% (95% CI, 9%–48%) for CHD, 44% (95% CI, 5%–83%) for PAD, and 45% (95% CI, 14%–76%) for stroke. For CHD, there remained evidence of a direct effect of urate even after adjusting for SBP (OR, 1.13 [95% CI, 1.03–1.23]; $P=0.01$). In contrast for PAD and stroke, although the estimate for the direct effect of urate that is not mediated through SBP was positive, the CI crossed the null and the results were not statistically significant (PAD: OR, 1.08 [95% CI, 1.00–1.17]; $P=0.07$; stroke: OR, 1.06 [95% CI, 0.99–1.12]; $P=0.10$). Direct effects of SBP on the outcomes after adjusting for genetically predicted serum urate are presented in Table S4.

There was no evidence of associations between genetically proxied CHD, PAD, stroke, or SBP with serum urate levels (Table S5). The results of the 1-sample MR analysis were consistent with the abovementioned 2-sample MR analysis and are detailed in Results in the [Data Supplement](#) and Tables S6 through S8. Results were similar for men and women in sex-stratified analyses (Results in the [Data Supplement](#)).

Systematic Review and Meta-Analysis of RCTs

In total, 92 studies were eligible for the systematic review and meta-analysis. Regarding the updated searches (January 1, 2016, to September 30, 2019), 5353 records were screened, 30 full texts were assessed for eligibility, and 13 studies were identified that fulfilled the eligibility criteria (Figure S7). Characteristics of included studies that were identified in the updated search are presented in Table S9.

The primary analysis of effects on SBP included 15 studies (Figure S8). The SD for mean SBP change pre- and post-treatment was only available for 1 study,²⁹ and this was used to impute the SD for mean SBP change pre- and post-treatment for the other studies.³⁰ There was heterogeneity between the 15 studies included ($I^2=89\%$), which was mostly attributable to 1 study considering renal dialysis patients that hid a high risk of bias (Table S10; Figure S8).³¹ Excluding this study, subjects treated with urate-lowering therapy had greater reduction in SBP than subjects in the control group (mean difference in SBP, -2.55 [95% CI, -4.06 to -1.05]; $P=1\times 10^{-3}$; $I^2=43\%$; Figure 4). The analysis of MACE risk in all patients considered 85 studies, of which 21 had events (Figure 5), and the analysis of MACE risk in patients with prior cardiovascular events considered 10 studies, of which 7 had events (Figure 6). Urate-lowering therapy was not significantly associated with risk of MACE in all patients (OR, 0.67 [95% CI, 0.44–1.03]; $P=0.07$;



Figure 2. Mendelian randomization estimates for the effect of 1-SD increase in genetically predicted serum urate levels on systolic blood pressure

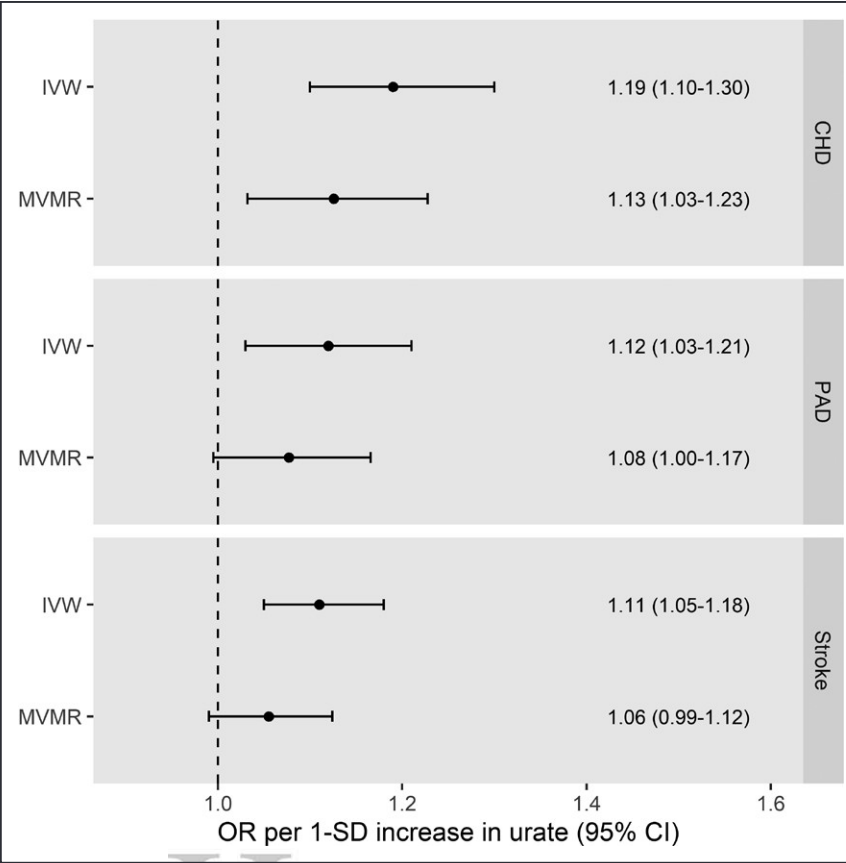


Figure 3. Inverse-variance weighted (IVW) and multivariable Mendelian randomization (MVMR) estimates for the effect of 1-SD increase in genetically predicted serum urate levels on risk of coronary heart disease (CHD), peripheral artery disease (PAD), and stroke.

The MVMR analysis adjusts for the associations of the genetic instruments with systolic blood pressure. The MVMR only adjusted for the associations of the genetic instruments with systolic blood pressure and not any other trait. OR indicates odds ratio.



$I^2=0\%$) but was significantly associated with reduction in risk of MACE in patients with a prior cardiovascular event (OR, 0.40 [95% CI, 0.22–0.73]; $P=3\times10^{-3}$; $I^2=0\%$). There was no evidence of heterogeneity between the estimates obtained from studies considering all patients

as compared with those restricted to patients with prior CVD (Cochran Q $P=0.11$).

Risk of bias was low in 16 of the 92 included studies (Table S10). Risk of bias was low in 1 of the 15 studies investigating effects on SBP, 16 of the 24 studies

Study name	Statistics for each study							Difference in means and 95% CI
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Alshahawi, 2017	-1.100	4.521	20.441	-9.961	7.761	-0.243	0.808	
Gingles, 2019	-0.590	1.886	3.556	-4.286	3.106	-0.313	0.754	
Gunawhardana, 2017	-0.300	1.712	2.933	-3.656	3.056	-0.175	0.861	
Kimura, 2018	-4.100	0.863	0.744	-5.791	-2.409	-4.753	0.000	
McMullan, 2017	-0.900	1.199	1.437	-3.249	1.449	-0.751	0.453	
Segal, 2015	-4.200	1.945	3.781	-8.011	-0.389	-2.160	0.031	
Higgins, 2014	-7.400	4.380	19.181	-15.984	1.184	-1.690	0.091	
Dogan, 2011	3.000	2.688	7.226	-2.269	8.269	1.116	0.264	
Karabay, 2011	-4.300	2.027	4.110	-8.273	-0.327	-2.121	0.034	
Goicoechea, 2010	0.000	2.153	4.635	-4.220	4.220	0.000	1.000	
Momeni, 2010	-2.200	2.619	6.859	-7.333	2.933	-0.840	0.401	

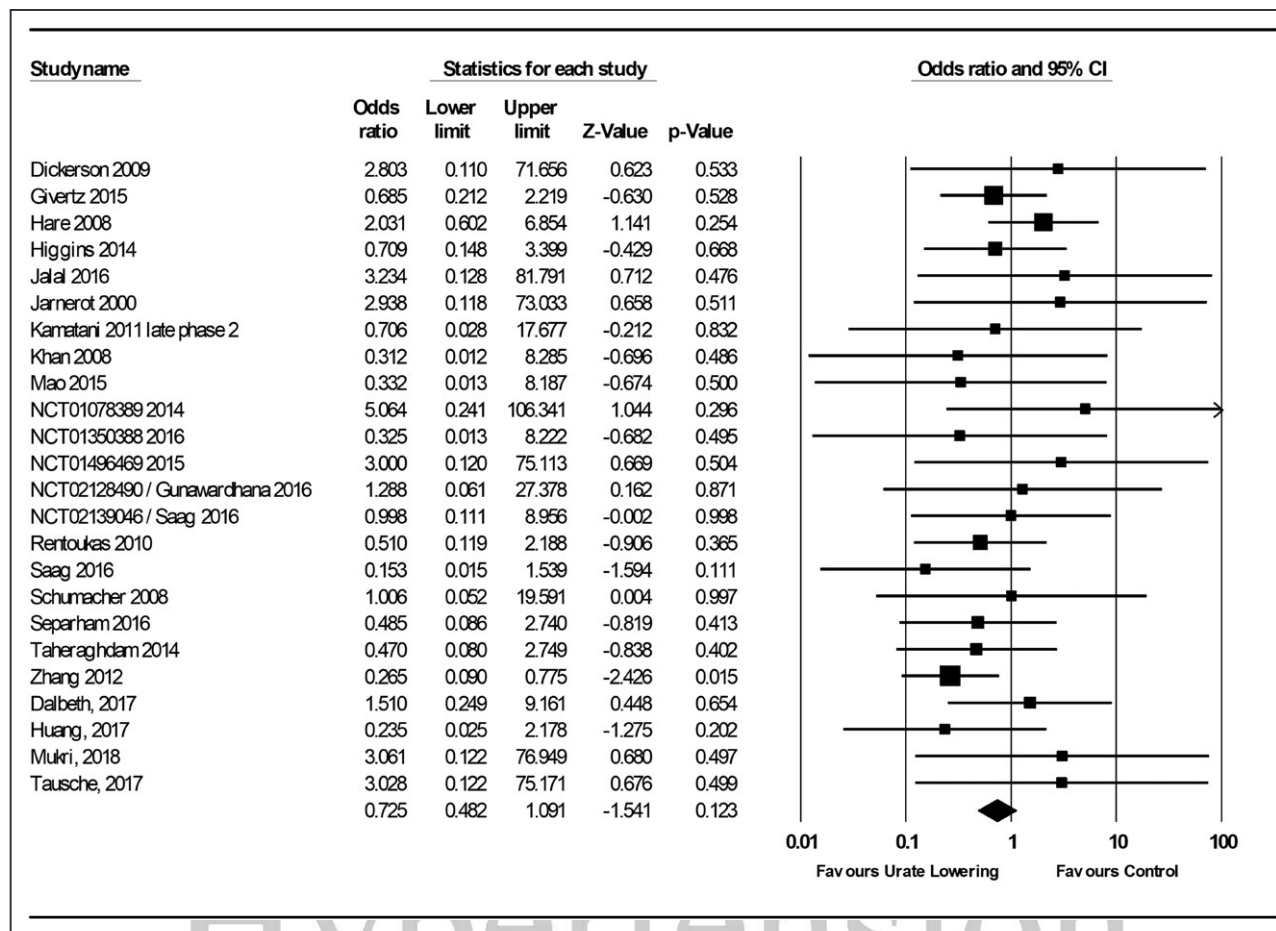


Figure 5. Forest plot of randomized controlled trial estimates for risk of major adverse cardiovascular events in all patients receiving urate-lowering therapy or placebo/no treatment.

I^2 heterogeneity statistic: 0%. A random-effects meta-analysis model was used.

investigating MACE in all patients, and 2 of the 7 studies investigating MACE in patients with a prior cardiovascular event. In sensitivity analyses including only studies at low-risk bias, urate-lowering therapy was not significantly associated with greater SBP lowering compared with control (mean difference in SBP, -7.40 [95% CI, -15.98 to 1.18]; $P=0.09$), MACE in all patients (OR, 0.64 [95% CI, 0.28 – 1.46]; $P=0.29$; $I^2=0\%$; Figure S9), or MACE in patients with a prior cardiovascular event (OR, 0.59 [95% CI, 0.18 – 1.91]; $P=0.38$; $I^2=0\%$; Figure S10).

Meta-regression analysis demonstrated no association of baseline SBP with SBP change following urate-lowering therapy (coefficient, -0.01 [95% CI,

S12). Meta-regression did not identify an association of absolute change in serum urate concentration ($P=0.63$) or proportional change in serum urate concentration ($P=0.59$) with SBP change with urate-lowering therapy. Meta-regression did not identify an association of baseline serum urate concentration ($P=0.96$), absolute change in urate concentration ($P=0.71$), or proportional change in serum urate concentration ($P=0.45$) with change in MACE risk with treatment with urate-lowering therapy.

DISCUSSION

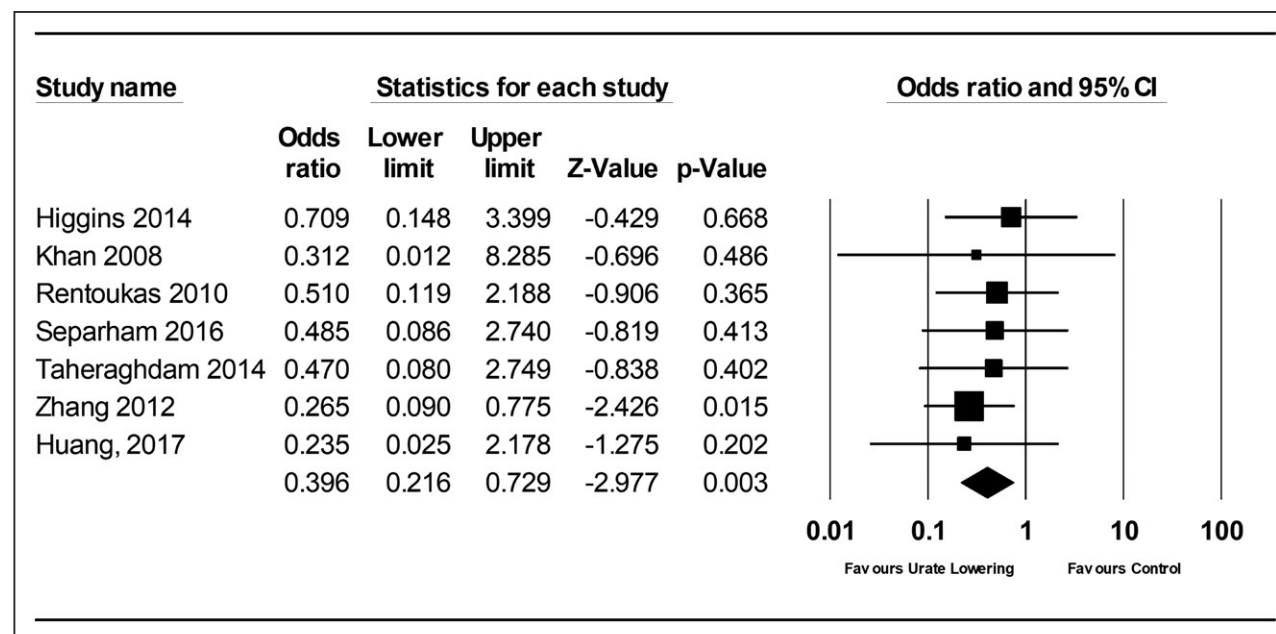


Figure 6. Forest plot of randomized controlled trial estimates for risk of major adverse cardiovascular events in patients with existing cardiovascular disease receiving urate-lowering therapy or placebo/no treatment.

I^2 heterogeneity statistic: 0%. A random-effects meta-analysis model was used.

SBP. Performing multivariable MR to adjust for genetic association with SBP attenuated the estimates for the CVD outcomes to support that at least some of the effect of urate may be mediated through raised blood pressure. Updated systematic review and meta-analysis of RCT data similarly showed a favorable effect of urate-lowering treatment on SBP, with meta-regression supporting a greater effect in individuals with higher baseline urate. There was also some trial evidence to support a protective effect on MACE risk in individuals with prior CVD.

Hyperuricemia has been postulated to cause endothelial dysfunction by increasing oxidative stress,¹ and this could directly increase risk of CVD through effects on the vascular endothelium.¹ In an animal model where hyperuricemia was induced using a uricase inhibitor, hypertension followed after 3 weeks while controls remained normotensive,⁸ thus representing a second mechanism by which urate can increase risk of CVD. The results of the FAST (Febuxostat and Allopurinol Streamlined Trial) and HEART trials (Allopurinol and Cardiovascular Outcomes in Patients With Ischaemic Heart Disease) will help provide further insight on potential repurposing of

the genetic instruments for urate with blood pressure as representing genetic confounding.^{3,5-7} Exclusion of such variants or adjustment for their genetic association with blood pressure traits, as was done in these studies,^{3,5-7} would obscure any true causal effect of genetically predicted urate on CVD risk. Our present MR analysis also incorporated more powerful instruments for serum urate than were available previously. The variants used as instruments in our 1-sample MR analysis of UK Biobank participants explained $\approx 7.7\%$ of the variance in serum urate,⁴ in contrast to the 5.3% that would be explained if selecting instrument variants from the previous largest published GWAS of serum urate.¹³ To further advance on previous MR efforts,^{3,6} our study also incorporated formal mediation analyses to investigate blood pressure as a mediator in the effect of serum urate on CVD risk. Similarly, our systematic review and meta-analysis of RCTs updated evidence from previous efforts to consider an additional 13 studies.^{10,11}

Study Limitations

to the strength of the urate instruments being correlated to their direct effects on the CVD outcomes under consideration.^{4,35} The genetic analyses were also based predominantly on individuals of European ancestry and thus may not apply to other populations or settings. Finally, use of urate-lowering mediation was not accounted for in MR analyses. Considering the meta-analysis of RCTs, the majority (76 of 92) of studies had a high or undetermined risk of bias, and there was heterogeneity in the results of RCTs measuring change in SBP following urate-lowering therapy, possibly related to study design, in turn limiting the strength of conclusions that can be drawn. Renal dialysis patients were not included in the MR analyses, and these results may, therefore, not apply to such populations. Finally, it may be that the identified effect of urate lowering on MACE in meta-analysis of trials considering patients with previous CVD but not in all patients or when restricting to studies with low risk of bias was attributable to insufficient statistical power.

Perspectives

We have found consistent MR and RCT evidence for an effect of higher serum urate levels on increasing SBP, with further evidence also supporting a potential effect on risk of CVD. High-quality trial data are now necessary to provide definitive evidence on the specific clinical contexts where urate lowering may be of cardiovascular benefit, with some large-scale studies already underway.^{32,33}

ARTICLE INFORMATION

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Disclosures

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